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EXAMINER

WHITEMAN, BRIAN A

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 111703

Application Number: 09/964,678
Filing Date: September 28, 2001
Appellant(s): MONTE ET AL.

Frank Cottingham

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/9/03.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) *Status of Claims*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(4) *Status of Amendments After Final*

No amendment after final has been filed.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

Appellant's brief includes a statement that claims 7, 8, 9, 14, 15, 16, and 35-40 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) *Claims Appealed*

Art Unit: 1635

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) *Prior Art of Record*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Ngo et al, The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495

Chui et al., Folding and Design, vol3, (1998), pp. 223-228

Polejaeva et al, Theriogenology, vol53, (2000), pp.117-126

Rulicke, Exp. Physiol. vol85, (2000), pp. 589-601

Trojanowski, Brain Pathology vol9, (1999), pp. 733-739

Wall, Theriogenology, vol45, (1996), pp. 57-68

Houdebine, J. Biotechnology vol34, (1994), pp. 269-287

Mullins, J. Clin. Invest, vol97, (1996), pp. 1557-1560

Strojek, Genetic Engineering: Principles and Methods, vol10, (1988), pp. 221-246

de la Monte, J. Neuropathol. Exp. Neurol, vol60, (2001), pp. 195-207

(10) *Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

Claims 7, 9, 14, 16, 35 and 36 are rejected under 35 U.S.C. 112 written description. This rejection is set forth in prior Office Action, Paper filed on 4/8/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

Art Unit: 1635

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 14, 16, 35 and 36 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7, 9, 14, 16, 35 and 36, as best understood, are readable on a genus of a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells, wherein the genus of DNA molecules is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The specification contemplates a genus of DNA molecules that code for a protein having the activity of SEQ ID NO: 1, which induces neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a host which expresses the DNA sequence for use in producing a transgenic non-human animal (page 18, lines 28-30 and page 20, lines 1-2). The specification provides sufficient description of SEQ ID NO: 1 and a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2. The specification provides sufficient description for a DNA molecule that codes for an AD7c-NTP protein when over-expressed in isolated neuronal cells. The art of record teaches that there is a variation within the genus of the claimed DNA molecules. The art of record further teaches that one nucleotide change in a DNA molecule could result in the loss of its biological activity. The

Art Unit: 1635

essential nucleotides required for an activity of AD7c-NTP are absent from the specification.

The specification does not provide sufficient description of a genus of DNA molecules with 90% homology to SEQ ID NO: 1 that codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. It is not apparent that on the basis of the applicants' disclosure an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of DNA sequences that must exhibit the disclosed biological functions as contemplated by the specification.

It is not sufficient to support the present claimed invention directed to a genus of a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of DNA molecules which is at least 90% homologous thereof, that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying

Art Unit: 1635

characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a DNA molecule, which displays at least 90% homology to SEQ ID NO: 1 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 7-9, 14-16, 35 and 36 remain and claims 37-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification discusses that the invention features a genus of transgenic non-human animals, which over-expresses a DNA molecule set forth in SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto and goes on to contemplate that there are techniques available for producing transgenic animals (page 20). The specification requires that the starting material, which is a nucleic acid set forth in SEQ ID NO. 1 or a DNA molecule which is at least

Art Unit: 1635

90% homologous thereto, be used in a method of making a transgenic non-human animal comprising over-expressing SEQ ID NO: 1 or a sequence with 90% homology thereto. The specification contemplates that the transgenic animals can be used in a method for identifying compounds that could be potential useful for the treatment or prevention of Alzheimer's disease (AD) (page 21). In addition, the specification states that, "SEQ ID NO: 1 is observed in patients with (AD)".

As stated above, the specification requires the claimed DNA molecule for producing transgenic non-human animals. In view of In Re Wands Factors, the specification teaches one skilled in the art how to make a DNA molecule comprising the nucleotide sequence set forth in SEQ ID NO: 1 or comprising a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2. The specification does not provide sufficient guidance or factual evidence for one skilled in the art to practice the full scope of the claimed invention. The specification does not disclose which nucleotides of the claimed DNA molecule is considered essential for one skilled in the art to make a representative number of DNA molecules with 90% homology to SEQ ID NO: 1. In view of the art of record and the as-filed specification, it is apparent that one skilled in the art would be able to determine a DNA molecule with 90 percent homology to SEQ ID NO: 1. However, the specification does not provide sufficient guidance or factual evidence for one skilled in the art to determine without an undue amount of experimentation to determine if the nucleic acid sequence with at least 90 percent homology to SEQ ID NO: 1, would exhibit the same biological function of SEQ ID NO: 1 (observed activity when the sequence is over-expressed in neuronal cells). Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et

Art Unit: 1635

al. The protein folding problem and tertiary structure prediction, 1994, Merz et al (ed.) Birkhauser, Boston, MA pp. 433 and 492-495 and Chiu et al., *Folding and Design*, 1998, pp. 223-228, cited on a prior 892), it would required undue experimentation for one skilled in the art to arrive at other DNA molecules with 90% homology to SEQ ID NO: 1 and having SEQ ID NO: 1 activity when over-expressed in neuronal cells. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other nucleotide sequences that are embraced by the claims. This is the case here. In other words, since it would require undue experimentation to identify other DNA sequences with at least 90% identity to SEQ ID NO: 1 and retaining the biological activity of SEQ ID NO: 1, it certainty would require undue experimentation to make their corresponding DNA and, therefore, one skilled in the art would not enabled to make a genus of DNA molecules with 90% homology to SEQ ID NO: 1. Therefore, the specification only provides sufficient guidance for making a DNA molecule comprising a nucleotide sequence set forth in SEQ ID NO: 1 or a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2.

In addition, the as-filed specification does not provide sufficient guidance or factual evidence for using the DNA molecule for making a transgenic non-human animal expressing a

Art Unit: 1635

nucleotide sequence encoding SEQ ID NO: 1 or a DNA molecule, which is at least 90% homologous thereto, and any corresponding phenotype.

It is further to note that the art of record at the time application was filed for producing transgenic animals with a predictable phenotype was considered unpredictable as exemplified by Polejaeva et al. *Theriogenology*, Vol. 53, pages 117-126, 2000, Polejaeva states:

Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. See page 119.

In view of the concerns set forth by the art of record, the specification does not reasonably address the concerns put forth by the art of record encompassing any method for producing transgenic animals for use in over-expressing SEQ ID NO: 1 or a sequence with 90% homology to SEQ ID NO: 1 with a corresponding phenotype. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification to any transgenic non-human animal over-expressing SEQ ID NO: 1 or a nucleotide sequence with 90% homology thereto.

In addition, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a DNA sequence set forth in SEQ ID NO: 1 is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any transgenic non-human animal. Furthermore,

Art Unit: 1635

each non-human animal comprises a distinct genome and the specification does not provide sufficient guidance for how to avoid random integration of a DNA molecule set forth in SEQ ID NO: 1, which would result in the characteristics contemplated in the specification. In addition, Trojanowski teaches that certain characteristic can be produce in a test tube, the conditions required are highly artificial and in vitro paradigms have limited utility as models of in vivo mechanisms of neurodegeneration (Brain Pathology, Vol. 9, page 737, 1999). Thus, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from a human having AD that endogenously over-expresses AD7c-NTP to a transgenic non-human animal expressing AD7c-NTP with a desired phenotype because of the art of record and the distinct genomic structure of each non-human animal.

In addition, the specification fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic non-human animals comprising a transgenic sequence encoding SEQ ID NO: 1 or a sequence with 90% homology thereto, which over-expresses the transgenic sequence such that a phenotype occurs. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any contemplated transgenic non-human animal of the invention when the nucleotide sequence is over-expressed in said animal. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic animal over-expressing SEQ ID NO: 1 or a sequence with 90% homology thereto.

[Note that although the claimed transgenic animal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the

claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic animal would serve if the transgene (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human animals as claimed, one skilled in the art would not be able to rely on the art of record for an attempt to produce any transgenic animals. This is because the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animal comprising a transgene of interest (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto) as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a

particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states “Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior.” See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic animal using microinjection of transgene into germ line and producing a transgenic animal which comprises a transgenic sequence encoding SEQ ID NO: 1 or a sequence with 90% homology thereto and which over-expresses the protein in the transgenic animal, and, thus, a specific resulting phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that “a given construct may react very differently from one species to another.” See page S39, Summary. Wall et al. report “transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies.” See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 239-239). Given

such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic animal that over-expresses SEQ ID NO: 1 or a sequence with 90% homology thereto, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic animal comprising a transgenic sequence set forth in SEQ ID NO: 1 or a sequence with 90% homology thereto and which over-expresses the protein in the transgenic animal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype.

Thus, in view of the *In re Wands*' Factors, the specification is not enabled for the claimed invention because in view of the undue quantity of experimentation necessary to determine the parameters listed above for the starting material, the lack of direction provided by the as-filed specification for the production of any transgenic non-human animal with a particular phenotype when a nucleotide with 90% homology to SEQ ID NO: 1 is over-expressed in said non-human animal. Furthermore, the lack of working examples for the demonstration or the reasonable correlation to the production of any transgenic non-human animal, in particular when the over-expression of the SEQ ID NO: 1 must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human animals of any species, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

Claims 7, 8, 9, 14, 15, 16, 35, 36, 37, 38, 39 and 40 are rejected under 35 U.S.C. 112 enablement. This rejection is set forth in prior Office Action, Paper filed on 4/8/2003. See above.

(11) Response to Argument

The examiner does not agree with the appellants grouping of the claims 7, 8, 9, 14, 15, 16, 36-40 under 112 first paragraph enablement into separate groups. Claims 7, 8, 9, 14, 15, 16, and 35-40 embrace a transgenic animal. All of the pending claims are rejected under enablement for making and/or using the claimed transgenic animal.

With respect to appellants' argument that, "Although the specification does not identify any particular nucleotides of SEQ ID NO: 1 as being "essential," the specification nonetheless provides a thorough description of the sequence characteristics and motifs in the amino acids sequence encoded by SEQ ID NO: 1 (see pages 11-12)," the argument is not found persuasive because the specification does not provide sufficient description for what nucleotides or amino acids are required for a genus of DNA molecules with 90% homology to SEQ ID NO: 1 that have an activity of AD7c-NTP when over-expressed in neuronal cells. The specification and drawings display that the amino acid sequence encoded by SEQ ID NO: 1 has (1) the hydrophobic leader sequence, (2), the myristoylation, (3) **potential** AI cleavage sites, (4) region of **homology** insulin/IGF-1 chimeric receptor, (5) **potential** glycogen synthesis kinase-3, protein kinase C and cAMP or Ca-dependent kinase II phosphorylation motifs (6) the transforming growth factor motif, (7) the sequence exhibit significant **homology** with the A4 alternatively spliced mutant form of NF2, the beta subunit of integrin and the human decay accelerating factor 2 precursor and (8) the sequences that exhibit **significant homology** with human integral membrane protein and myelin oligoglycoprotein-16 (page 7, line 21 through page 8, line 3 of the specification). The specification does not provide sufficient description for what characteristic(s) listed above result in an activity of AD7c-NTP when over-expressed in neuronal cells. More

Art Unit: 1635

specifically, the specification does not provide sufficient description for how an assertion that the sequence has a **potential** AI cleavage sites or has a **potential** glycogen synthesis kinase-3, protein kinase C and cAMP or Ca-dependent kinase II phosphorylation motifs represents sufficient description of a genus of claimed DNA molecules. Furthermore, the specification does not provide sufficient description for how the sequence having homology or significant homology to a protein (e.g., glycogen synthesis kinase-3, protein kinase C and cAMP or Ca-dependent kinase II phosphorylation motifs, integral membrane protein, myelin oligoglycoprotein, etc.) represents sufficient description of a genus of claimed DNA molecules. The specification does not provide sufficient description that the proteins listed above have an activity of Ad7c-NTP selected from neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles and irregular swollen neurites. There is no known correlation in the specification and the art of record between the function and structure set forth in the claims to the proteins listed on pages 7 and 8 in the specification.

With respect to appellants' argument that, "the situation presented in Example 14 of the Written Description Synopsis closely parallels the DNA molecules that are used with or are included within the subject matter of Appellants' claims and the written description provided therefor (See pages 12-16)," the argument is not found persuasive. The argument is not found persuasive because the specification in example 14 is directed to a protein that catalyzes the reaction of $A > B$ and the claim recites a protein having SEQ ID NO: 3 and variants that are least 95% identical to SEQ ID NO: 3 and catalyzes the reaction of $A > B$. Appellants claims recite a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto, wherein said DNA molecules is over-expressed in one or more cells of said transgenic animal

Art Unit: 1635

and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. The instant claims recite at least 90% homologous thereto, while the claim in Example 14 recites variants thereof that are at least 95% identical to SEQ ID NO: 3. 90% homology is different than 95% homology. There are 1,442 nucleotides in SEQ ID NO: 1. 90% homology is a nucleotide sequence with up to 144 different nucleotides and 95% homology is a nucleotide sequence with up to 72 different nucleotides. Furthermore, Example 14 is directed to a protein that catalyzes a specific reaction and the instant claims do not recite a protein that catalyzes a specific reaction. The as-filed specification does not provide sufficient description that the amino acid encoded by SEQ ID NO: 1 catalyzes any reaction. In addition, the as-filed specification does not provide sufficient description for procedures for making variants of SEQ ID NO: 1, which has 90% homology and retains an activity of AD7c-NTP when over-expressed in neuronal cells. The USPTO written description guidelines for Example 14 do not correlate to the written description in the appellants' specification as asserted by applicants. Therefore, the as-filed specification does not provide sufficient description for a genus of nucleotide sequences with up to 144 different nucleotides (90% homology) to SEQ ID NO: 1 and possesses the biological activity of SEQ ID NO: 1 (AD7c-NTP) when over-expressed in neuronal cells.

With respect to appellants' arguments that, "in *Enzo*, the Federal Circuit also made specific reference to Example 9 of the Written Description Synopsis. See *Enzo*, 296, F.3d at 1328, 63 USPQ2d at 1615. The analysis set forth in Example 9 further supports Appellants' contention that the written description requirement is satisfied for the claims involved in this appeal and that the rejection was made in error (pages 16-18)," the argument is not found

Art Unit: 1635

persuasive. The argument is not found persuasive because Example 9 is directed to an isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclases activity. The DNA molecule set forth in the claimed invention is not directed to a nucleic acid that encodes a protein that binds a receptor and stimulates a specific activity. Example 9 does not correlate to the applicants' specification.

Thus, the as-filed specification does not provide sufficient description for a genus of nucleotide sequences with up to 144 different nucleotides (90% homology) to SEQ ID NO: 1 and possesses the biological activity of SEQ ID NO: 1 (AD7c-NTP) when over-expressed in neuronal cells.

With respect to appellants' arguments that, "it would only require routine experimentation for a skilled artisan to obtain the DNA molecules that are used to produce the transgenic animals of the invention. See Section VIII.C.(a)(i)" and "the Examiner has not presented sufficient evidence or scientific reasoning to support the rejection (pages 30-31)," the argument is not found persuasive because in view of the In Re Wands Factors, the specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a genus of a DNA molecule that is 90% homologous to SEQ ID NO: 1. The amino acid encoded by SEQ ID NO: 1 (1,442 nucleotides) has 375 amino acids (SEQ ID NO: 2). The claims are broader than the enabling disclosure because there is no guidance as to which (if any) of the 375 amino acids may be changed while AD7c-NTP is retained. The total number of 375 amino acid peptides is 8.475×10^{65} . The number of single amino acid substitutions is 7,125. The number of two amino acid substitutions is over 50,000,000. The claims embrace a

Art Unit: 1635

nucleotide sequence that is 90% homologous to SEQ ID NO: 1 and SEQ ID NO: 1 has 1,442 nucleotides. Since the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and predictable (e.g., see Ngo et al, in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require undue experimentation for one skilled in the art to arrive at other 375 peptides that have AD7c-NTP activity when over-expressed in neuronal cells. For example, a deletion or a substitution of one amino acid or nucleotide could result in a polynucleotide with at least 90% sequence identity to SEQ ID NO: 1, but not encoding a functional Ad7c-NTP protein. In addition, if you replace the nucleotide at each wobble position in the polynucleotide sequence set forth in SEQ ID NO: 1, the polynucleotide sequence would not have at least 90% sequence identity to SEQ ID NO: 1, but would have 100% amino acid sequence identity. The specification and the art of record are absent for the teaching that it is routine to correlate predicting a peptide's activity based on its nucleotide sequence.

Furthermore, the as-filed specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen 8.475×10^{65} amino acid peptide for peptides that meet or do not meet the limitations set forth in the claims. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states:

Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements, while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in

Art Unit: 1635

cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The specification does not provide sufficient guidance and/or factual evidence that it was routine to substitute or delete up to 144 nucleotides of a 1,442 nucleotide sequence and determine without undue experimentation, which nucleotide sequences meet the functional limitation of the claims.

Furthermore, with respect to appellants' arguments that the examiner has not explained why it is believed that the production of DNA molecules that are included within the transgenic animals of the invention would require the identification of "essential nucleotides (pages 30-31)," is further not found persuasive because an article (Exhibit 3, Sambrook et al., eds. Cold Spring Harbor Laboratory Press, pp. 15.95, 1989) provided for support provided by appellants supports the unpredictability of making a DNA molecule with 90% homology to the DNA molecule set forth in SEQ ID NO: 1. Sambrook supports the 112 enablement rejection because Sambrook teaches that, "at present, it is impossible to predict with accuracy the effect of substituting one amino acid for another in a protein" and "when the number of desired mutants exceeds 20 or so, it becomes impractical and expensive to generate each of them individually (See Exhibit 3)." As stated above, the specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen 8.475×10^{65} amino acid peptide for peptides that meet or do not meet the limitations set forth in the claims.

With respect to the appellants' argument that, "the Examiner statement regarding the identification of "essential" nucleotides does not support a rejection for lack of enablement (pages 31-32)," is not found persuasive because without the "essential" nucleotides of SEQ ID NO: 1 for AD7c-NTP activity when over-expressed in neuronal cells, it would require an undue

Art Unit: 1635

amount of experimentation for one skilled in the art to arrive at other DNA molecules with 90% homology to SEQ ID NO: 1 and having AD7c-NTP activity when over-expressed in neuronal cells. As stated above, the total number of 375 amino acid peptides (the amino acid SEQ ID NO: 2 encoded by SEQ ID NO: 1 has 375 amino acids) is 8.475×10^{65} . The specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen 8.475×10^{65} amino acid peptide for peptides that meet or do not meet the limitations set forth in the claims. The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.

In re Vaeck, 947 F.2d 48, 496 & n.23, 30 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a “plan” or “invitation” for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation for experimentation in view of the art of record exemplifying the unpredictability of making and using any DNA molecule with 90% homology to SEQ ID NO: 1 that has an activity of AD7c-NTP when over-expressed in neuronal cells, for those skilled in the art to experiment with DNA molecules with 90% homology to SEQ ID NO: 1 to produce a genus of claimed DNA molecules as intended by the as-filed specification at the time the invention was made.

With respect to appellants’ arguments that, “The examiner has not explained why it is believed that the production of DNA molecules within the transgenic animals of the invention would have required a skilled artisan to predict the relationship between the sequence of a peptide and its structure” and “the examiner’s statements relating to the ability of a skilled

Art Unit: 1635

artisan to predict the relationship between the sequence of a peptide and its structure do not support a rejection for lack of enablement (pages 32-33),” is not found persuasive because if the peptide does not have AD7c-NTP activity when over-expressed in neuronal cells, then one skilled in the art would not be enabled to practice the claimed invention. The specification does not provide sufficient guidance for one skilled in the art to use a DNA molecule with 90% homology to SEQ ID NO: 1, wherein the DNA molecule encodes a peptide, wherein the peptide has AD7c-NTP activity when over-expressed in neuronal cells. Since the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and predictable (e.g., see Ngo et al, in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require undue experimentation for one skilled in the art to arrive at other 375 peptides that have AD7c-NTP activity when over-expressed in neuronal cells. For example, a deletion or a substitution of one amino acid or nucleotide could result in a polynucleotide with at least 90% sequence identity to SEQ ID NO: 1, but not encoding a functional Ad7c-NTP protein. In addition, if you replace the nucleotide at each wobble position in the polynucleotide sequence set forth in SEQ ID NO: 1, the polynucleotide sequence would not have at least 90% sequence identity to SEQ ID NO: 1, but would have 100% amino acid sequence identity. The specification does not provide sufficient guidance for one skilled in the art to determine what DNA molecules with 90% homology to SEQ ID NO: 1 have or do not have AD7c-NTP when over-expressed in neuronal cells. Appellants’ assertion (pages 32-33) that screening for molecules that possess a particular activity (AD7c-NTP activity) is both common and routine in the biological arts is not supported by any evidence. At the time the application was filed

(provisional was filed on 2/26/97), the specification does not provide sufficient guidance and/or factual evidence that it is routine to screen 8.475×10^{65} peptides and determine without an undue amount of experimentation which peptides meet or do not meet the limitations set forth in the claims.

With respect to appellants' argument that, "the reasons set forth in *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991) for finding the claims non-enabled cannot be used to support a rejection of the present claims for lack of enablement (page 33)," the argument is not found persuasive because the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other nucleotide sequences that are embraced by the claims. This is the case here. In other words, since it would require undue experimentation to identify other DNA sequences with at least 90% identity to SEQ ID NO: 1 and retaining the biological activity of SEQ ID NO: 1, it certainly would require undue experimentation to make their corresponding DNA and, therefore, one skilled in the art would not enabled to make a genus of DNA molecules with 90% homology to SEQ ID NO: 1. Therefore, the specification only provides sufficient guidance for making a DNA molecule comprising a nucleotide sequence set forth in SEQ ID NO: 1 or a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2.

With respect to Appellants' arguments that, "claims 7-9, 14-16, 35, 36, 39, and 40 do not require that the transgenic animal exhibit a specific phenotype (pages 34-37)," the argument is

not found persuasive because in view of the In Re Wands Factors, the specification does not teach one skilled in the art how to use a transgenic non-human animal without a phenotype. The specification contemplates using a non-human animal in a screening method for candidate drugs that are potentially useful for treatment or prevention of Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas. Furthermore, the specification recites that the candidate drug will cause the suppression or prevention of expression of the protein; the increased degradation of the protein; or the reduction of frequency of at least one sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons in the animal. In view of the guidance taught in the specification (page 21, line 12), it is not apparent to one skilled in the art how to use a transgenic animal with no phenotype (e.g., it does not express a phenotype observed with Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas in neuronal cells). The specification and art of record art are absent that cells other than neuronal cells are involved in Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas. [Note that although the claimed transgenic animal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other

purpose the transgenic animal would serve if the transgene (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto) is not expressed at a sufficient level for a resulting phenotype).] The specification (page 21, lines 14-17) and art of record are absent to the teaching that the reduction of frequency of at least one sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons are observed in non-neuronal cells. In view of these facts and the fact that the claimed transgenic animals does not exhibit a phenotype indicia specific to Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas and the only disclosed utility for the claimed transgenic animal is a model of Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas so as to screen candidate agents which can be used as therapeutic agents, the specification fails to teach how to use the claimed transgenic mouse without a phenotype without an undue amount of experimentation.

With respect to appellants' arguments that, "drugs can be identified on the basis of their ability to increase the degradation of the protein encoded by the DNA molecule contained by the transgenic animal" and "Candidate drugs can be identified by their ability to cause, e.g., the suppression or prevention of expression of the protein encoded by the DNA molecule contained in the transgenic animal," is not found persuasive because the specification lacks sufficient guidance for one skilled in the art to use a transgenic animal set forth in claim 7 if the transgenic animal does not display a phenotype observed in Alzheimer's disease and/or brain tumors. The specification does not teach that the claimed transgenic animal without a phenotype correlates to an animal model for Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas. The specification and the art of record lack sufficient guidance or evidence for

Art Unit: 1635

reasonably correlating identifying a drug that increases degradation of the protein encoded by the DNA molecule contained in the animal without a phenotype to the drug being a candidate drug for Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas. The art of record is absent for teaching how to use a transgenic animal with no phenotype in a method for screening drugs for a disease (e.g., Alzheimer's Disease). Thus, if the transgenic animal has no phenotype correlated with Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas, then it would take one skilled in the art an undue amount of experimentation from detecting one of the following characteristics listed in step b) (i) and (ii) of claim 14 using the transgenic animal with no phenotype and reasonably correlating that the drug is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas.

With respect to appellants' arguments that, "The examiner has not set forth sufficient evidence to indicate that producing transgenic animals with a specific phenotype would have required undue experimentation (pages 38-49)," the argument is not found persuasive because in view of the In Re Wands Factors, the specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to practice the claimed invention. At the time the application was filed (provisional filed on 2/26/1997), the art of record teaches the unpredictability of predicting a desired phenotype in a transgenic animal over-expressing a protein in neuronal cells. Rulicke (Experimental Physiology, Vol. 85, pages 589-601, 2000) teaches that, "the generation of transgenic animals through microinjection of naked DNA is particularly difficult and not yet routinely applicable." Mullins (J. Clin. Invest., Vol. 97, pages 157-1560, 1997) teaches that, "germline transmission has only been achieved with mouse ES

Art Unit: 1635

cells” and “The major problem regarding pronuclear microinjection is that the exogenous DNA integrates randomly into chromosomal DNA.” The breadth of the claims embrace making and using any animal in the claimed invention. There is no working example of a transgenic non-human animal comprising somatic and germ cells comprising the DNA molecule set forth in SEQ ID NO: 1 or a DNA molecule with 90% homology thereto with no phenotype or a desired phenotype set forth in the specification. The specification and art of record are absent for how to predict a desired phenotype when the exogenous DNA integrates randomly into the animal’s chromosomal DNA without an undue amount of experimentation. The art of record is absent for producing a transgenic animal comprising somatic and germ cells comprising the DNA molecule set forth in SEQ ID NO: 1 or a DNA molecule with 90% homology thereto when over-expressed in neuronal cells. The specification does not provide sufficient guidance or evidence for one skilled in the art in the art to make the claimed transgenic animals and determine, which animal embraces or does not embrace the functional limitations set forth in the claims without an undue amount of experimentation.

With respect to appellants’ arguments that, “There is no indication that the experimentation needed to successfully obtain a transgenic animal with a particular phenotype using pronuclear microinjection would be *undue*” and “Polejaeva indicates that somatic cell nuclear transfer -- a method that would have been available to one of ordinary skill in the art as of the effective filing date -- is another method that is **likely** to be successful in the production of transgenic animals with a particular phenotype,” the argument is not found persuasive because of the reasons set forth above and in view of the lack of sufficient guidance and/or factual evidence for making and using the transgenic animal, it would take one skilled in the art an undue amount

of experimentation to practice the claimed invention. Furthermore, the effective filing date of the application is 2/26/97 and the assertion that, "somatic cell nuclear transfer is likely to be successful," is not supported by the as-filed specification because the specification does not provide sufficient guidance and/or factual evidence that somatic cell nuclear transfer was routine to one skilled in the art for producing the claimed transgenic animal with a predicting phenotype.

Furthermore, with respect to appellants' arguments that, "Trojanowski does not support the position of the claimed invention is not enabled (pages 41-42)," the argument is not found persuasive because the goal of Trojanowski was to produce an animal model that displayed filamentous tau inclusions (page 736, left column) and Trojanowski did not produce animals with filamentous tau inclusions. Instead, the animals showed pre-tangle tau pathology.

Furthermore, with respect to appellants' arguments that, "it is incorrect to assert that the specification fails to provide "any relevant teachings or sufficient guidance" regarding the production of the transgenic animals of the invention (pages 42-43)," is not found persuasive because the art of record teaches the unpredictability of predicting a desired phenotype when expressing a transgene in an animal. The specification provides no working example for making and/or using the claimed transgenic non-human animal. The art of record is absence for producing a transgenic non-human animal having a DNA molecule of SEQ ID NO: 1 or a DNA molecule, which is at least 90% homologous thereto. The specification fails to provide sufficient guidance and/or factual evidence that producing the claimed transgenic non-human animal was well known in the art.

Furthermore, with respect to appellants' arguments that, "various phenotypes associated with the transgenic animal of the invention are described in the specification are described in the

Art Unit: 1635

specification (pages 43-44),” is not found persuasive because the specification provides no working example with the phenotypes cited in the specification in the claims. As stated above, the art of record displays the unpredictability of producing a desired phenotype in a transgenic animal. The neuritic abnormalities cited in the specification are observed in post mortem humans. The support for the claimed phenotype is based on an in vitro experiment with isolated neuronal cells that are not in contact with other cells or cell products that might be required for the observed phenotype observed in humans with Alzheimer’s Disease (page 46). Trojanowski teaches that, “certain characteristics produced in a test tube, [but] are highly artificial an in vitro paradigms have limited utility as models as in vivo mechanisms of neurodegeneration (page 733-739). The specification does not teach if other gene product(s) present/not present in the neuronal cells used in the in vitro experiment are involved in observing the neuritic abnormalities in vivo. An in vitro system does not allow one skilled in the art to study physiological system in its entirety. The art of record is absent for teaching whether the neuronal cells used in the in vitro experiment reasonably correlate to predicting the claimed phenotype.

With respect to appellants’ arguments (pages 44-48) directed to exhibits (journal articles) displaying the production of transgenic animals with a desired phenotype correlates to producing the claimed transgenic non-human animals with no phenotype or a certain phenotype, the argument is not found persuasive because each of the exhibits use distinct materials not contemplated or taught by the instant specification. The exhibits do not teach producing the claimed transgenic non-human. Several of the exhibits cited for support for predicting a desired phenotype indicative of Alzheimer’s disease support the unpredictability of predicting a desired phenotype. While, it is acknowledged that there are other types of transgenic animals cited in the

Art Unit: 1635

art that use distinct materials (different gene, different disease, etc.) and methods, the art of record teaches that one skilled in the art can not reasonably extrapolate from one transgenic animal to another type of transgenic animal without an undue amount of experimentation and the art of record teaches that there is not universal protocol that can be reasonably extrapolated from making one type of transgenic animal to the claimed transgenic animal.

Wirak teaches, “evidence of neuronal cell death, early signs of CNS dysfunction have been not detected in transgenic mice at 1 year of age (page 324).” See Exhibit 8. The as-filed specification lacks sufficient guidance and/or evidence for one skilled in the art to reasonably correlate from the transgenic animals with different phenotypes taught in the art at the time the application was filed to making the claimed transgenic animal without an undue amount of experimentation. This observation is supported by Wall (Theriogenology, 1996) who states “Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior.” See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The claimed phenotype for Alzheimer’s disease may require gene product(s) in neuronal cells, including the AD7c-NTP gene product that are not taught by the specification. Wirak teaches that, “the data raise the possibility that amyloid beta protein expression alone is not sufficient to produce amyloid accumulation (page 324).” See Exhibit 8.

Furthermore, with respect to appellants’ arguments that de la Monte (exhibit 18) supports practicing the claimed invention (pages 48-49), the argument is not found persuasive because de

Art Unit: 1635

la Monte teaches that they were unable to study AD7c-NTP overexpression because initial studies resulted in depletion of neuronal cells in culture. In view of de la Monte, one skilled in the art would conclude that if over-expression of AD7c-NTP results in neuronal cell death *in vitro* than the claimed animal would die before birth or soon after birth because of neuronal cell death and would not be available for use in the claimed screening assays. The specification fails to provide sufficient guidance for how to use an animal before the animal dies from depletion of neuronal cells.

Furthermore, with respect to the appellants' assertion that, "There is no evidence that over-expression of AD7c-NTP in non-neuronal cells would result in cell depletion (page 49)." The assertion is not found persuasive because the specification and art of record do not provide sufficient guidance and/or evidence that over-expression of AD7c-NTP in non-neuronal cells would/would not result in cell depletion.

For the above reasons, it is believed that the rejections should be sustained.

Art Unit: 1635


Respectfully submitted,

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